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| 10/666,722 | 09/18/2003 | Lee Martin Greenberger | AM101032 | 9014 |

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| EXAMINER | |
|---|---|
| JEAN-LOUIS, SAMIRA JM | |
| **ART UNIT** | **PAPER NUMBER** |
| 1627 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/666,722 | GREENBERGER ET AL. | |
| | Examiner | Art Unit | |
| | SAMIRA JEAN-LOUIS | 1627 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *60-66,68,72-79,81 and 82* is/are pending in the application.

4a) Of the above claim(s) *67 and 80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-66, 68, 72-79 and 81-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Arguments*

This Office Action is in response to the amendment submitted on 07/20/09. Claims 60-68 and 72-82 are currently pending in the application, with claims 1-59 and 69-71 having being cancelled and claims 67 and 80 having being withdrawn. Accordingly, claims 60-66, 68, 72-79, and 81-82 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Applicant's argument with respect to the objection of claim 25 has been fully considered. Given the cancellation of claim 25, such objection is now moot. Consequently, the objection to claim 25 is hereby withdrawn.

Applicant's arguments that the claims are limited to tumors resistant to at least one chemotherapeutic agent and thus do not pertain to all cancers have been fully considered but are not found persuasive. The Examiner again reiterates the fact that tumors of various tissues (i.e. breast, colon, etc...) possess contrasting etiologies and pathophysiologies. Specifically, the Examiner contends that because tumors can be so different, what kills one type of tumor cell might not do anything to another. As a result, treatment of one tumor resistant to at least one chemotherapeutic agent does not

translate into treatment of all tumors resistant to at least one chemotherapeutic agent. However, given that applicant has cancelled and amended the claims, the rejection of claims 1-7, 9-57, 59-66, 68, 73-79 and 81 under 35 U.S.C. § 112, first paragraph is hereby withdrawn.

As for applicant's arguments that according to the MPEP, chapter 2164.03, even in unpredictable arts, a disclosure of every operable species is not required and that representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in a manner without undue experimentation have been fully considered but are not found persuasive. The Examiner again reiterates that in the case of the instant invention one of ordinary skill in the art would not expect that the compounds of formula II would be effective in every tumor resistant to at least one chemotherapeutic agent. As a result, the Examiner contends that undue experimentation would indeed be needed in order to determine if the compounds of formula II can in fact treat, inhibit or eradicate all tumors of all etiologies that are resistant to at least one chemotherapeutic agent. Thus, because adequate reasons were presented by the Examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation, proof of enablement was therefore required for other members of the claimed genus. While applicant argues that numerous experiments were performed demonstrating that certain tumors effectively responded to some compounds of formula II, the Examiner maintains that not all compounds were effective and not all tumors were tested. Moreover, in view of the fact that cancer is complex and multifactorial, the

Examiner contends that one of ordinary skill in the art at the time of the invention would have indeed concluded that all compounds of formula II could not result in effective treatment of all tumors resistant to at least one chemotherapeutic agent. However, given applicant's amendment and cancellation of the claims, such rejection is hereby withdrawn.

Applicant's argument that applicants have demonstrated the ability of the claimed compounds to inhibit cell growth in a myriad of tumor cell lines has been fully considered but is not found persuasive. The Examiner respectfully points out that while compound 57 was taught in the Affidavit dated April 11, 2008 to be effective against colon, breast and melanoma cell lines, the Examiner maintains that the claims as previously presented was directed to all compounds of formula II and not just compound 57. Additionally, the Examiner maintains that in view of the contrasting etiologies and pathophysiologies of tumors, not all compounds of formula II will be effective in all tumors resistant to at least one chemotherapeutic agent. As a result of the unpredictability of the art, the Examiner maintains that enablement for the other compounds is needed since one of ordinary skill in the art would conclude that the treatment of tumor resistant to at least one chemotherapeutic agent with compounds of formula II would result in undue experimentation. However, given that applicant has amended and cancelled the claims, such rejection is hereby withdrawn.

Applicant's argument that Kowalczyk et al. provide no specific activity associated with the compounds disclosed in Kowalczyk has been fully considered. Applicant further argues that only a general statement regarding the compounds of formula I of Kowalczyk et al. was given in regard to their effectiveness in treating cancer and that only certain exemplary embodiments for the IC values were disclosed. Such arguments are not found persuasive as Kowalczyk et al. clearly delineated the use of the compounds in the treatment of cancer (see abstract). In fact, Kowalczyk et al. teach the compounds as novel Hemiasterlin analogs that are effective in the treatment of cancers including breast, colon, ovarian, and pancreatic cancers etc... (see col. 1, lines 64-67 and col. 2, lines 20-34). Moreover, Kowalczyk et al. tested various cell lines including the paclitaxel-resistant cell line DLD-1 and HCT-15 and suggest the effectiveness of these compounds. As a result, the Examiner maintains that Kowalczyk et al. do indeed render obvious applicant's invention. As for applicant's arguments that Kowalczyk et al. do not recited the amended claims, such arguments are not found persuasive as applicant is arguing features not previously presented. It is noted that the features upon which applicant relies (i.e., compounds 57 and 129) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). However, in view of applicant's cancellation and amendment of the claims, the rejection of claims 1-7, 9-57, 59-66, and 68 under 35 U.S.C. § 103(a) is hereby withdrawn.

For the foregoing reasons, the rejections of record were indeed proper. However, in view of applicant's amendment and cancellation, the following modified 112, first paragraph and 103 (a) Final rejections are being made.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-66, 68, 72-79, and 81-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compound 57 in the treatment of certain cancers such as breast, colon, melanoma in the treatment of tumors resistant to paclitaxel and vincristine, and compound 129 in the treatment of certain tumors resistant to paclitaxel, does not reasonably provide enablement for the aforementioned compounds in the treatment of every single tumor resistant to every single chemotherapeutic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating, inhibiting growth of, or eradicating a tumor in a mammal in need thereof wherein said tumor is resistant to at least one chemotherapeutic agent which method comprises providing to said mammal

an effective of compound 57 or 129 or pharmaceutically acceptable salts thereof. The instant specification fails to provide information that would allow the skilled artisan to practice the treatment of all tumors resistant to every single chemotherapeutic agent.

In re Sichert, 196 USPQ 209 (CCPA 1977)

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method of treating, inhibiting growth of, or eradicating a tumor in a mammal in need thereof wherein said tumor is resistant to at least one chemotherapeutic agent which method comprises providing to said mammal an effective of compound 57 or compound 129 or pharmaceutically acceptable salts thereof. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. Particularly, the examiner cites the fact that cancer is a complex disease wherein each tumors arising from cancer possess contrasting pathophysiology and contrasting etiology thereby rendering it impossible for one compound to treat every single tumor of contrasting etiology. Moreover, applicant claims treatment of all tumors regardless of the tumor origin as long as they are resistant to a chemotherapeutic agent, yet applicant's own limited *in vitro* data in the specification demonstrate that the aforementioned compounds

were not tested in gastric cancer, for example. These results thus raise serious doubt to one skilled in the art as to whether the aforementioned compounds are indeed effective in the treatment of all tumors resistant to at least one chemotherapeutic agent.

2. The breadth of the claims

The claims are thus very broad insofar as they recite the "treatment of all tumors" of various origins that are resistant to any chemotherapeutic agent. While such "treatment" might theoretically be possible *in vitro*, as a practical matter it is nearly impossible to achieve a treatment for tumors of all origins and that are resistant to all chemotherapeutic agents with the same compound.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for the treatment of mouth, or gastric tumors, for example, with the aforementioned compounds; yet applicant claims the treatment of such tumors. No reasonably specific guidance is provided concerning treatment of every single tumors of all tumor origins and resistant to all and any chemotherapeutic agents with the aforementioned compounds, other than melanoma, colon, breast, and epidermoid tumors. The latter is corroborated by the working examples in tables 1-12.

The instant disclosure provides no evidence to suggest that this unique activity can be extrapolated to gastric, for example, having unrelated mechanisms of resistance, and thus does not meet the "how to use" prong of 35 USC 112, first paragraph with regard

thereto.

Additionally, applicant failed to provide enablement for the treatment of the elected cancer species, ovarian tumors using compound 57.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed compounds could be predictably used for the treatments of all tumors resistant to any chemotherapeutic agents as inferred by the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

***Claim Rejections - 35 USC § 103***

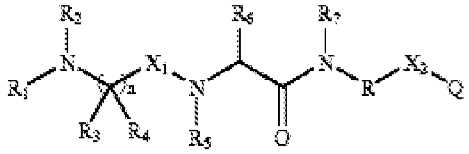
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 60-66, 68, and 72 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kowalczyk et al. (U.S. 7,064,211 B2, previously cited).**

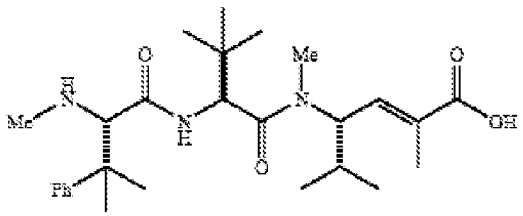
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Kowalczyk et al. teach compounds of formula I;



and methods for the use thereof in the treatment of cancer (see abstract, col. 1, lines 65-67, and col. 4-5). Importantly, Kowalczyk et al. teach that the compounds of formula I demonstrate anti-tumor activity and can be made into pharmaceutical compositions or salts thereof for the treatment of various cancers including ovarian cancer (i.e. applicant's elected tumors; see col. 2, lines 20-33, col. 60, lines 30-35 and col. 103, lines 21-50). In particular, the compounds of formula I are taught by Kowalczyk to

exhibit growth inhibitory effect on cancer cell lines maintained in vitro or in animal studies using a scientifically acceptable cancer cell xenograft model; cause tumor regression in vivo; exhibit low sensitivity to MDR and low cytotoxicity and exhibit a favorable therapeutic profile (see col. 99, lines 53-64 and col. 101-102). Certain compounds of formula I according to Kowalczyk exhibit IC50 values less than or equal to 10 μM while others are in the range of 0.1nM-10nM (see col. 100, lines 40-67). Exemplary compounds of the invention include compound ER-804762 with the following structure:




which reads on applicant's compound 129 or N,ß,ß-trimethyl-L-phenylalanyl-N1-[(1S,2E)-3-carboxy-1-isopropylbut-2-enyl]-N1,3-dimethyl-L-valinamide (see col. 125, ER-804762). Kowalczyk et al. further teach that the compounds of the invention were tested in various cancer cell lines including the paclitaxel-inherent resistant cell lines DLD-1 and HCT-15 thus supporting the notion that such compounds are indeed effective in the treatment of paclitaxel resistant tumors (see col. 434, lines 1-21 and col. 436, lines 1-10).

Kowalczyk et al. do not specifically teach testing of compound 129 (i.e. claim 60). Likewise, Kowalczyk et al. does not teach administering such compounds after paclitaxel.

Kowalczyk et al. however does teach that compounds of the invention were tested in paclitaxel resistant cell lines such DLD-1 and HCT-15 and can be used for the effective treatment of cancer.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the compounds of Kowalczyk after treatment of paclitaxel in order to avoid tumor resistance. Moreover, one of ordinary skill in the art at the time of the invention would have indeed found it obvious to utilize ER-804762 in the treatment of ovarian tumors since Kowalczyk teaches the use of the compounds of the invention for the treatment of such tumors. Thus, given the teachings of Kowalczyk et al., one of ordinary skill in the art would have been motivated to utilize the disclosed compounds of Kowalczyk et al. in the treatment of ovarian tumors with the reasonable expectation of providing a method that is efficient in treating and reducing tumor growth including ovarian tumors.

## ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in

this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

11/22/2009

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627